Advances in Pharmacotherapy for Alcohol Dependence:

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Speaker Disclosures

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NOTICE

Non-FDA approved applications (off-label uses) of selected FDA-approved medications (disulfiram, ondansetron, topiramate) and data regarding non-FDA-approved medications (kudzu extract, naltrexone depot injection forms) will be discussed during this presentation. Use of medications for non-FDA-approved treatments should be disclosed to patients, together with risks, benefits, and alternative treatments, where available. Use of non-FDA-approved medications for treatment of health conditions is legal only under certain circumstances (e.g., approved research).

OBJECTIVES

- Rationale for Pharmacotherapy
- Rx approved prior to 2004: disulfiram, naltrexone
- Acamprosate
- Other Rx under study: topiramate, ondansetron, depot naltrexone, etc

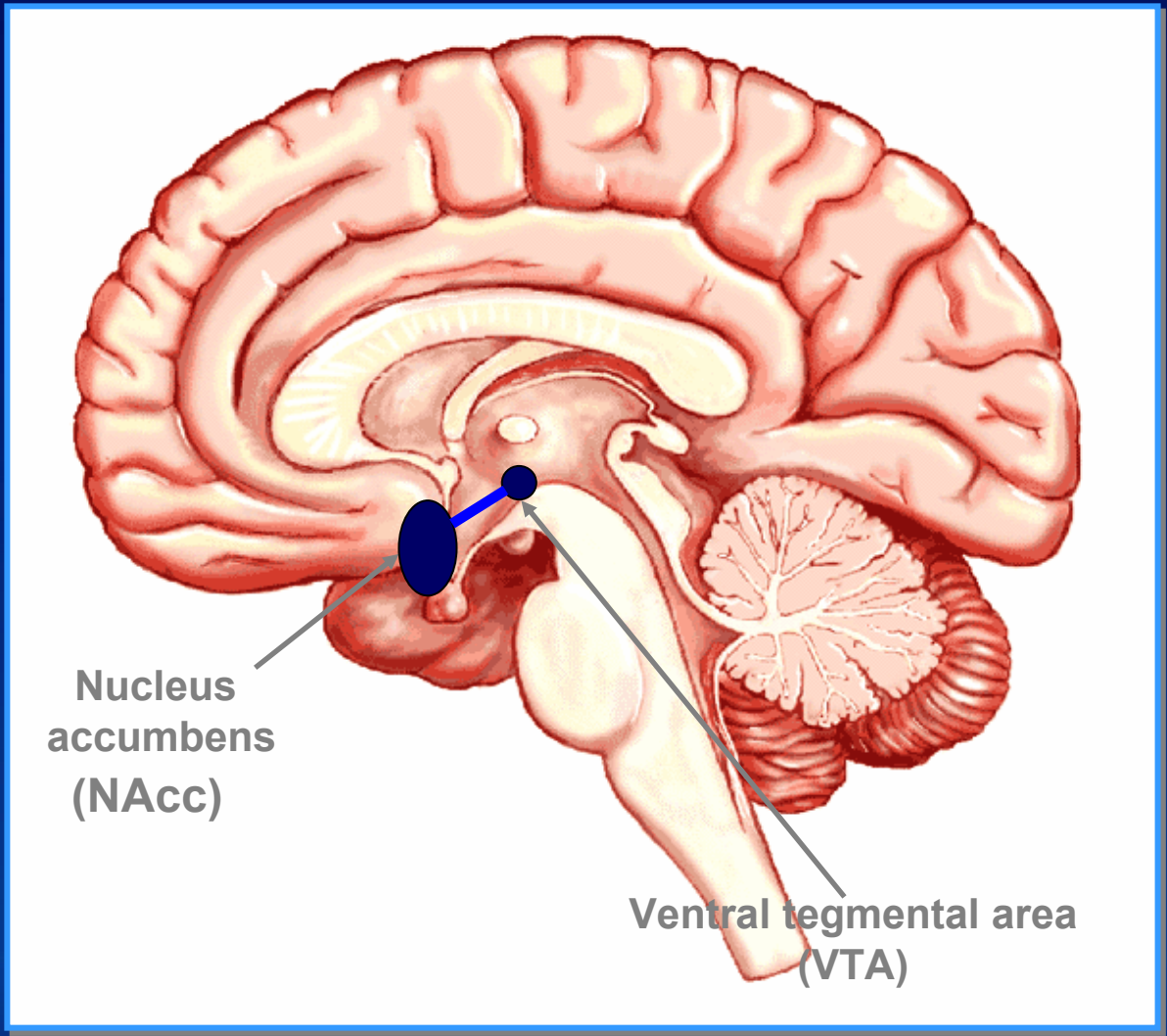
Rationale for Alcoholism Pharmacotherapy

Alcohol Catabolism: Protective Genes

$$CH_3CH_2OH \xrightarrow[ADH]{} CH_3CHO \xrightarrow[ALDH]{} CH_3COOH$$

- ALDH2*2 allele: best characterized genetic factor protecting against alcohol dependence
  - Low Km→ accumulate acetaldehyde→ flushing
- > 50% allele prevalence in Chinese, Korean, Japanese, other Asian populations, and some Jewish peoples
- Up to 70-80% abstinence among heterozygotes
- Near 100% abstinence for homozygotes

Brain Reinforcement Pathways



- Activated by addictive drugs & ethanol
  - Not by other Rx's
- Action potential trains release DA if more reinforcer received than expected
- Med. spiny neurons here connected to PFC (planning, + affect) hippocampus (memory) & amygdala (fear & - affect)
- Enhances learning of complex motor action sequences e.g., drug use, cued responses

Source: Messing RO. In: Harrison's Principles of Internal Medicine. 2001:2557-2561.

Effects of Acute Alcohol on Reward Circuits

Dopamine and Opioid Systems

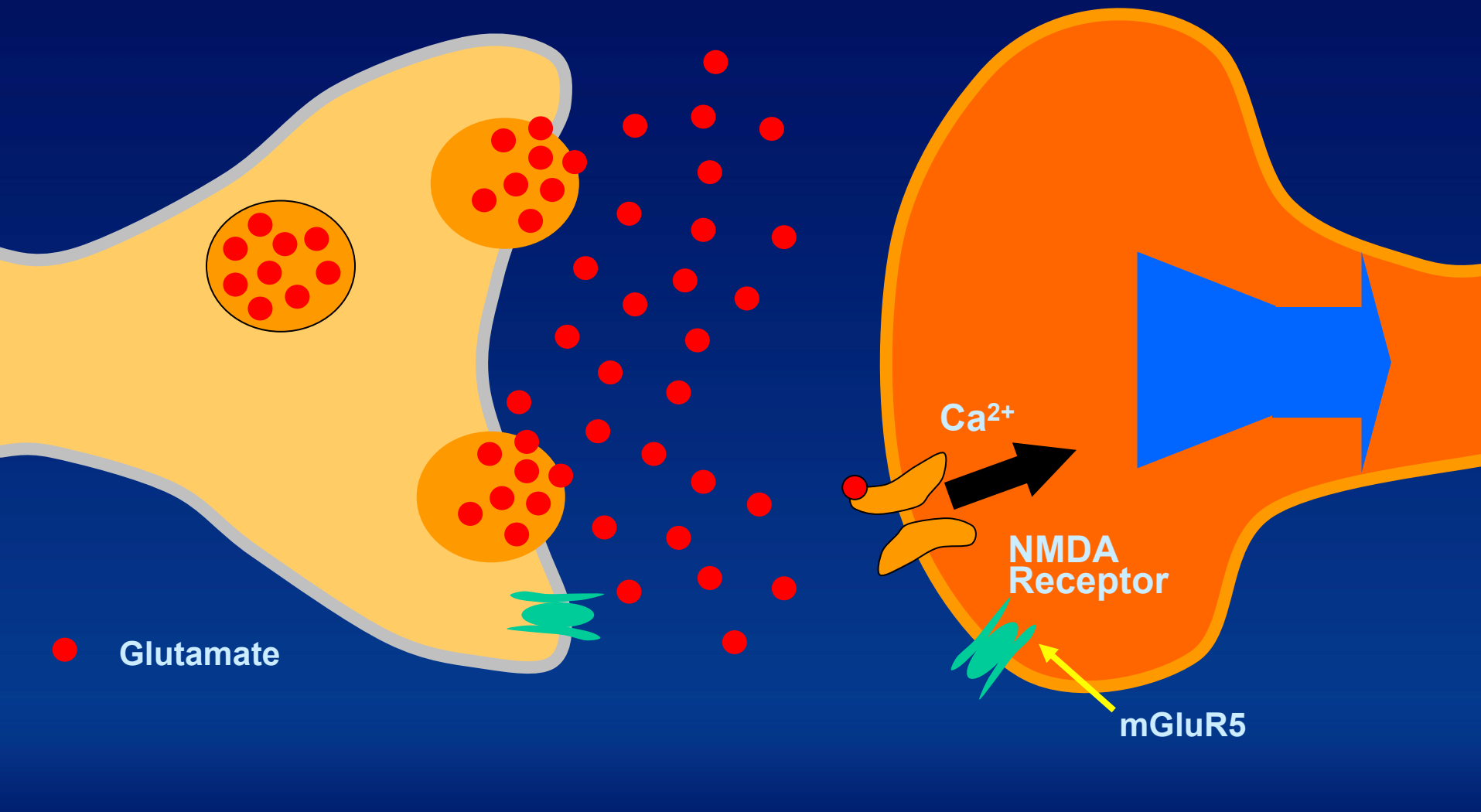
- **Indirectly activates opiate system via increasing met and leu enkephalin and endorphin**
- **These bind to μ and δ opiate receptors on inhibitory interneurons→ ↓firing→ ↑VTA medium spiny neuron DA release in NAcc.**
- **Pretreatment with μ opiate receptor antagonists naloxone or naltrexone blocks EtOH self-administration**

Sources: Koob GF, et al. *Neuron*. 1998;21:467-476.
Messing RO. In: *Harrisions Principles of Internal Medicine,* 15th ed. 2001:2557-2561.

Functions of Prefrontal Cortex

- Inhibiting automatic, previously rewarded behaviors
- Shifting attention to new cues
- Learning new or modified motor behaviors after a new or related cue
- Inhibiting amygdala and stress response
- Reducing consumptive behavior after satiety

Pathophysiology of Potential Relapse: Role of Glutamate



Acute Alcohol Intake: Glutamate, Opiate and DA effects

→ blunted glutamate effects via NMDA-induced
-- neuronal depolarization and action potentials
-- cGMP production
-- Ca^{++} entry
-- excitotoxicity

→ enhanced GABA effects→ sedation

→ Increased POMC transcription→ met, leu enkephalin→ IPSP in inhibitory interneurons → increased spike bursts, DA release in NAcc by medium spiny neurons → reinforcement learning

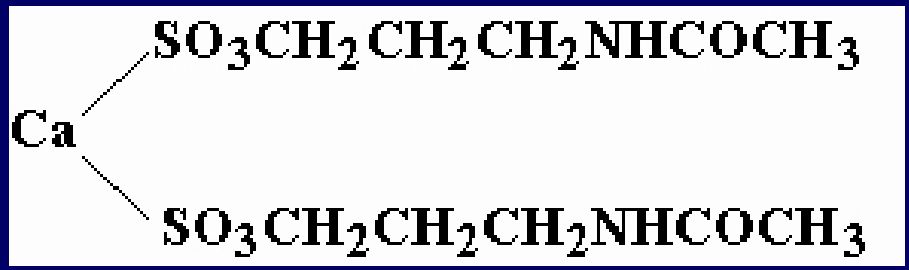
Chronic Ethanol Intake: Glutamate Effects

- Reduced blunting of NMDA-induced
  - Depolarization
  - cGMP production
  - Ca^{++} release
  - excitotoxicity
- *Increase in NMDAR's*
- *Increased synthesis of specific NMDAR subunits*
  - (NR1, 2A, 2B)
- *Increase in glutamate quanta sizes*

Ethanol Discontinuation: Glutamate Effects

- *decreased glutamate release*
- *NR2A & B subunit activation*→*
  - enhanced neuronal firing
  - * acamprosate may reduces this effect
  - activation may also affect seizures

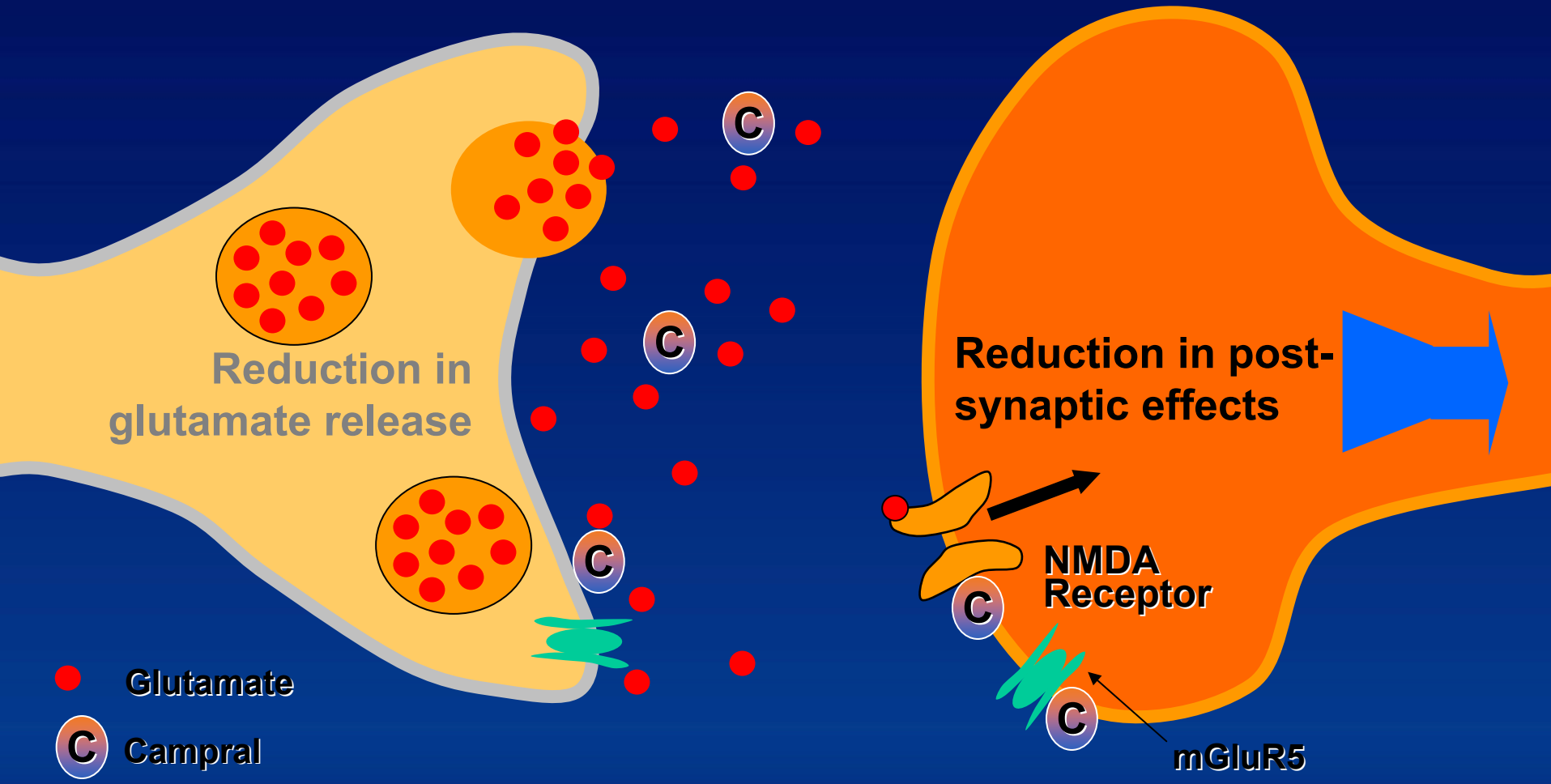
Acamprosate (Calcium N-acetylhomotaurinate)



- **Derivative of taurine, a CNS amino acid**
  $C_{10}H_{20}CaN_2O_8S_2$: MW = 400.48
- **Interacts w/ glutamate & GABA systems**
- **EtOH deprivation→ increased EtOH intake**
- **Acamprosate→ reduces deprivation effect**

Balancing Pathophysiology

Campral®



Effects of Acute Alcohol on Other Neural Circuits

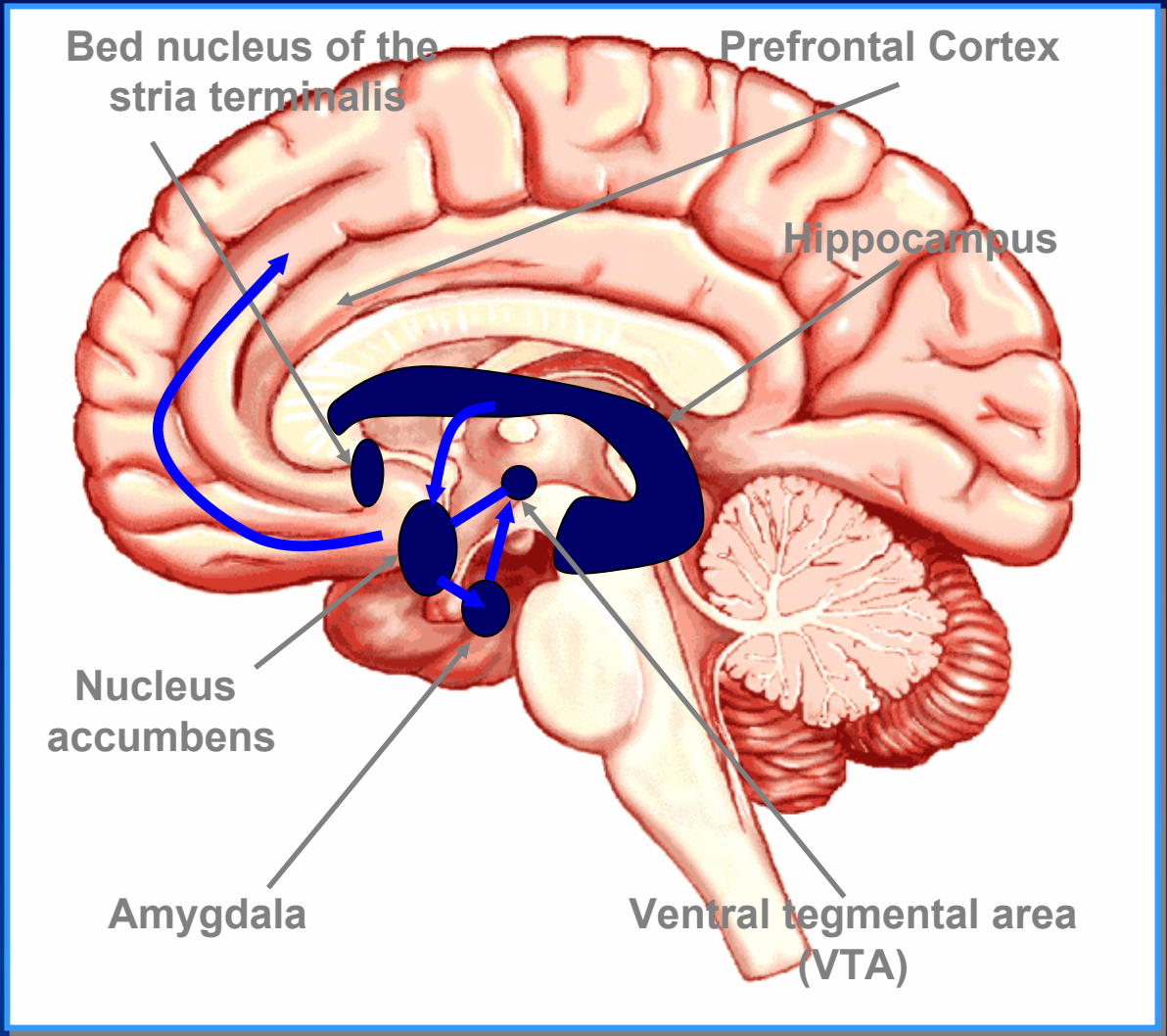
GABA and Glutamate Systems

- **Increases the effects of GABA, the major inhibitory neurotransmitter in the brain**
- **Inhibits the effects of glutamate, the major excitatory neurotransmitter in the brain**
- **Contributes to decreased anxiety and increased sedation during acute alcohol intake**

GABA = gamma-aminobutyric acid.

Source: Littleton J. *Alcohol Health Res World*. 1998;22:13-24.

Relapse and Conditioning



- Repeated alcohol use w/ cues can → "conditioning"
- Conditioned cues activate PFC genes
- Stress may substitute for cues
- Both may → reinstatement of use
- Use & cues may be associated with conditioned + or – affects

Source: Messing RO. In: Harrison's Principles of Internal Medicine. 2001:2557-2561.

Pharmacotherapies for Alcohol Dependence

FDA-Approved Pharmacotherapies for Alcohol Dependence Prior to 2004

Drug Class	*Comments*
Disulfiram (Antabuse®)	• Inhibits aldehyde dehydrogenase • When taken with alcohol, ↑ [acetaldehyde] leads to nausea, dizziness, headache, flushing • Inhibits CYP2D6→ Rx interactions (WARFARIN) • Poor compliance; best w/ spouse/P.O. help • Black box liver failure warning, safety issues
Naltrexone (ReVia®)	• Opioid antagonist • Binds to opioid receptors, thus blocking alcohol reward pathways • Black box warning, pain mgmt issues

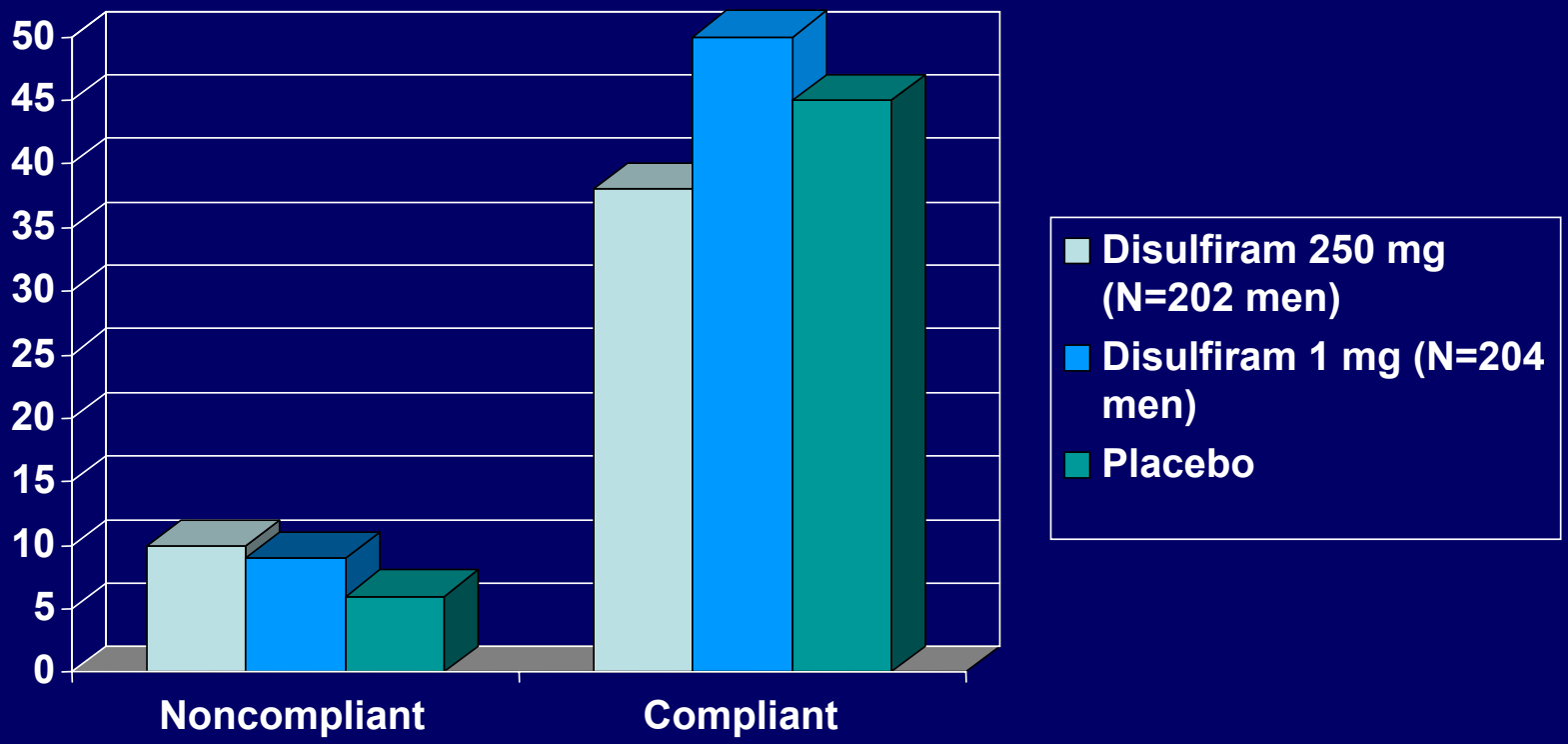
Antabuse® TM by Odyssey Pharmaceuticals, Inc.and ReVia® TM by DuPont Merck Pharmaceutical Company

Source: O'Connor PG, et al. *N Engl J Med*. 1998;338:592-602.

Disulfiram: The only Multisite RCT

- Fuller et al. Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. *JAMA.* 1986;256:1449.
- RESULTS
  - No significant differences in abstinence rates among groups taking placebo, disulfiram 1 mg/day, or disulfiram 250 mg/day
  - Compliant patients, regardless of group, reduced their alcohol consumption

Rate of Abstinence During Treatment with Disulfiram (VA Coop)



Fuller et al. *JAMA.* 1986;256:1449.

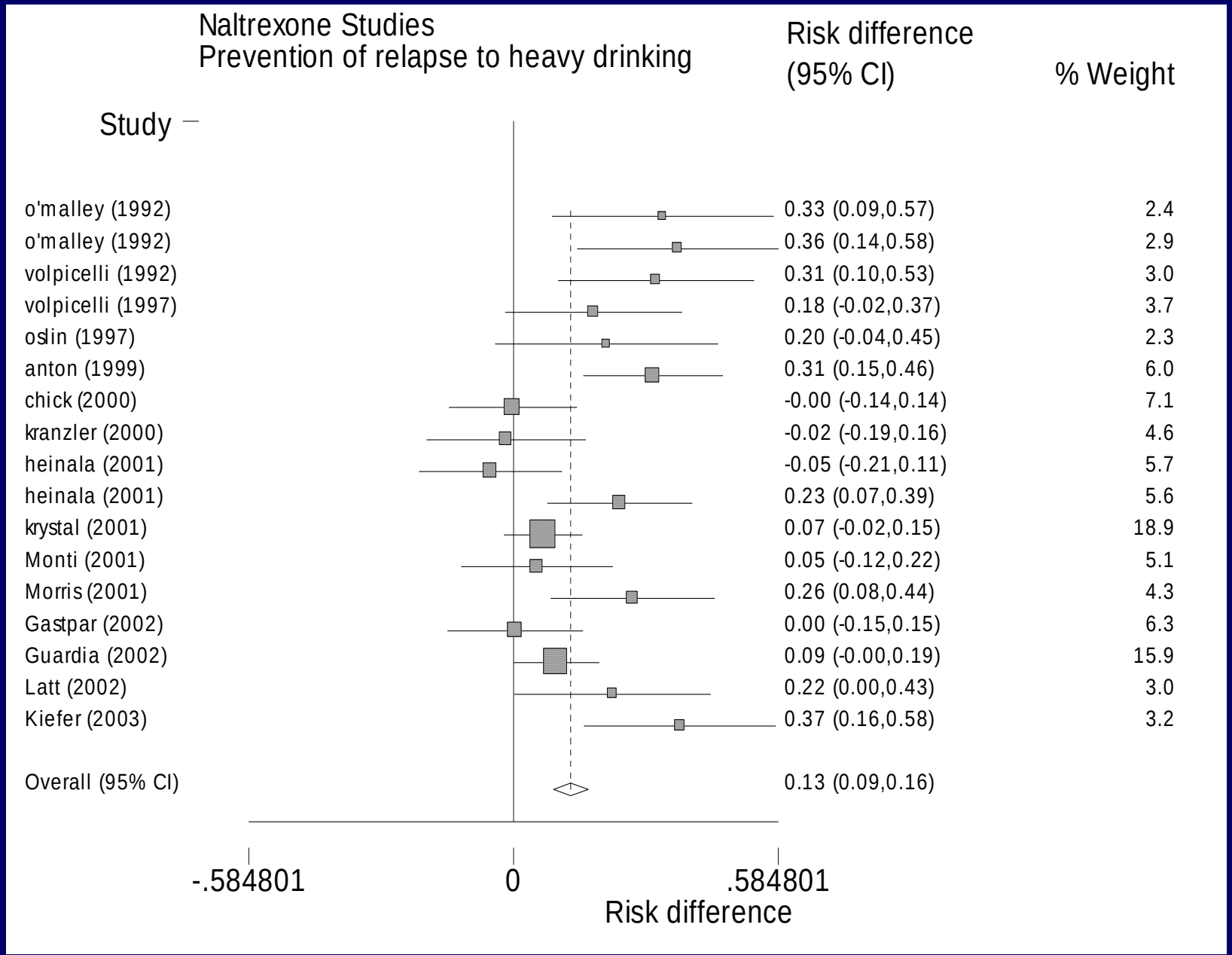
Disulfiram
Adverse Effects

- Common
  - Sedation, metallic taste, garlic odor
- Uncommon
  - Peripheral neuritis, polyneuritis, optic neuritis (rates low)
  - Psychosis @ high dose
  - Hepatitis, cholestatic jaundice, liver failure risk: 1/ 25,000 Black Box Warning
  - Allergic rxn: rubber allergy overlap

Disulfiram Research Update

- Compliance enhancement
  - Marital contracts effective
- Cocaine Dependence
  - 3 published RCTs
  - Reduced frequency of cocaine + UDS
  - Mechanism of action? DBH inhibition?
  - Effective in non-dependent drinkers who are cocaine dependent

O'Farrell et al. 2002, Carroll et all 2004


Naltrexone Studies
Prevention of relapse to heavy drinking
Risk difference
(95% CI)
% Weight
Study
o'malley (1992) 0.33 (0.09,0.57) 2.4
o'malley (1992) 0.36 (0.14,0.58) 2.9
volpicelli (1992) 0.31 (0.10,0.53) 3.0
volpicelli (1997) 0.18 (-0.02,0.37) 3.7
oslin (1997) 0.20 (-0.04,0.45) 2.3
anton (1999) 0.31 (0.15,0.46) 6.0
chick (2000) -0.00 (-0.14,0.14) 7.1
kranzler (2000) -0.02 (-0.19,0.16) 4.6
heinala (2001) -0.05 (-0.21,0.11) 5.7
heinala (2001) 0.23 (0.07,0.39) 5.6
krystal (2001) 0.07 (-0.02,0.15) 18.9
Monti (2001) 0.05 (-0.12,0.22) 5.1
Morris (2001) 0.26 (0.08,0.44) 4.3
Gastpar (2002) 0.00 (-0.15,0.15) 6.3
Guardia (2002) 0.09 (-0.00,0.19) 15.9
Latt (2002) 0.22 (0.00,0.43) 3.0
Kiefer (2003) 0.37 (0.16,0.58) 3.2
Overall (95% CI) 0.13 (0.09,0.16)
-.584801
0
.584801
Risk difference

Naltrexone Response Predictors

- Compliance
  - Depot forms under study
- Genetics
  - Mu Opiate Receptor structural gene

Oslin et. al. 2004

Naltrexone Adverse Effects

- Common
  - Nausea, anxiety, tremor, sweating, opiate blockade
- Uncommon
  - Worsening of pain
  - Increased LFTs at 300 mg daily Black Box Warning
  - Precipitated opiate withdrawal in active opiate addicts

Acamprosate Treatment of Alcohol Dependence

- By 2005, approved for alcohol dependence in Europe, Asia, Mexico, S. America, & US
- 15/18 European multisite RCTs in 13 countries (total *N* = 5000+) found abstinence increased 50%
- US multisite clinical trial results have been presented but are not yet published

Indications and Usage*

- **Campral® is FDA approved for**
  - **maintenance of abstinence**
  - **patients with alcohol dependence**
  - **When used in comprehensive management program w/ psychosocial support (no published tests)**

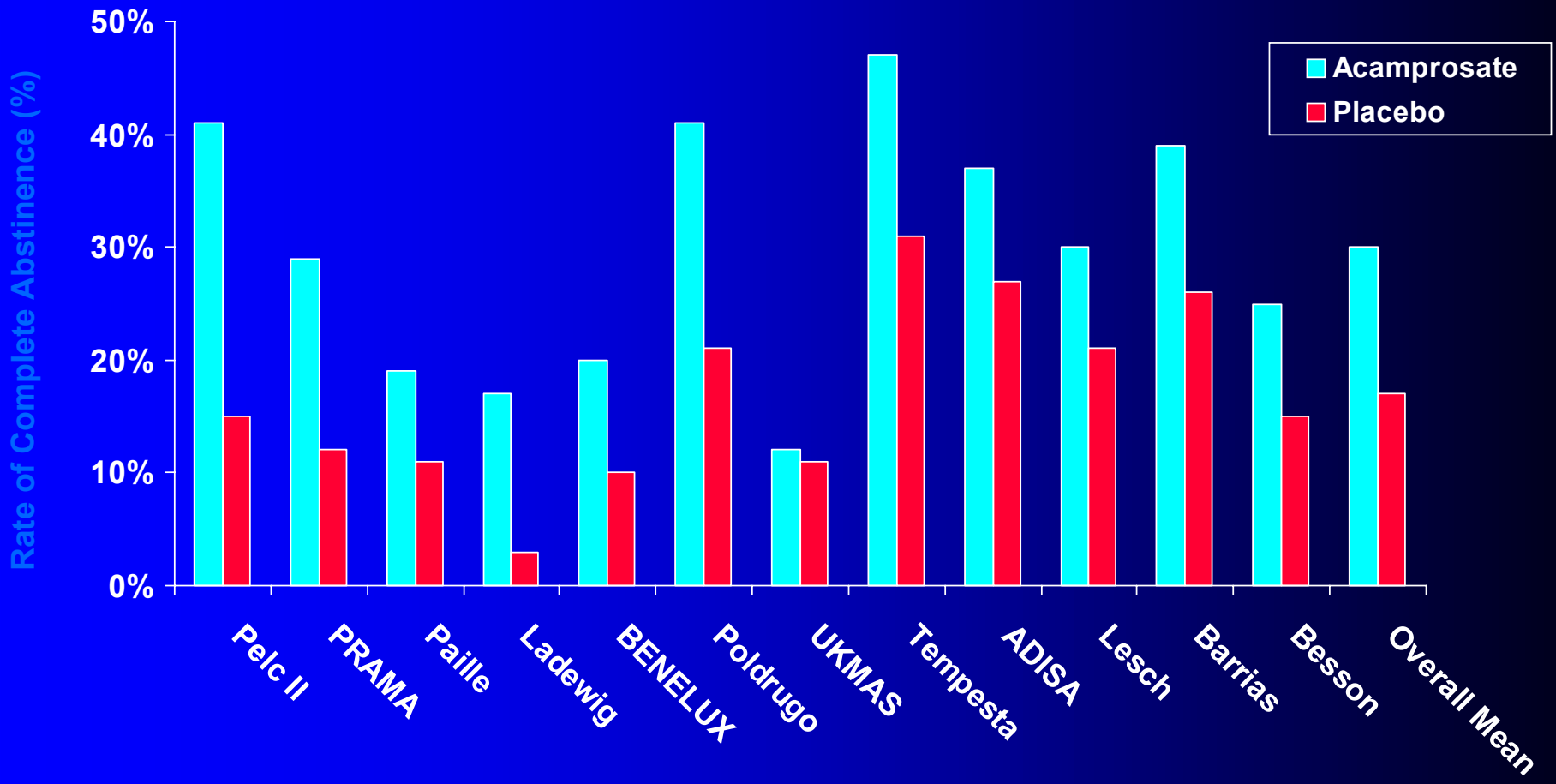
Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Acamprosate Pharmacodynamic Effects

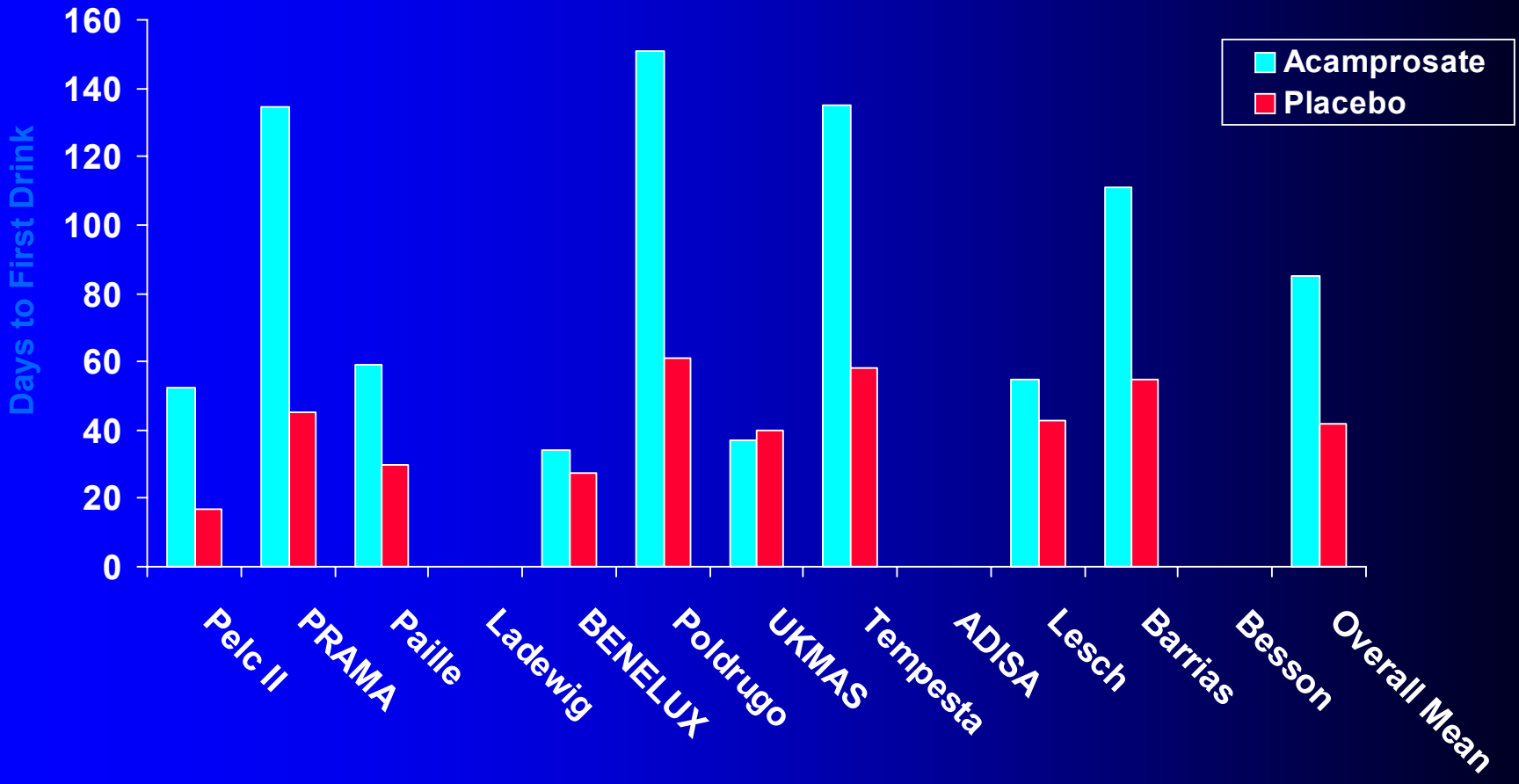
- **Unique mechanism of action in maintaining abstinence is not completely understood**
- **Chronic alcohol exposure is thought to alter normal balance between neuronal excitation and inhibition**
- **Campral is believed to act on the biochemical systems that are involved in alcohol dependence**
  - **_In vitro_ and _in vivo_ studies in animals suggest acamprosate may interact with glutamate and GABA neurotransmitter systems to restore balance**

Campral is a registered trademark of Merck Santé
Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

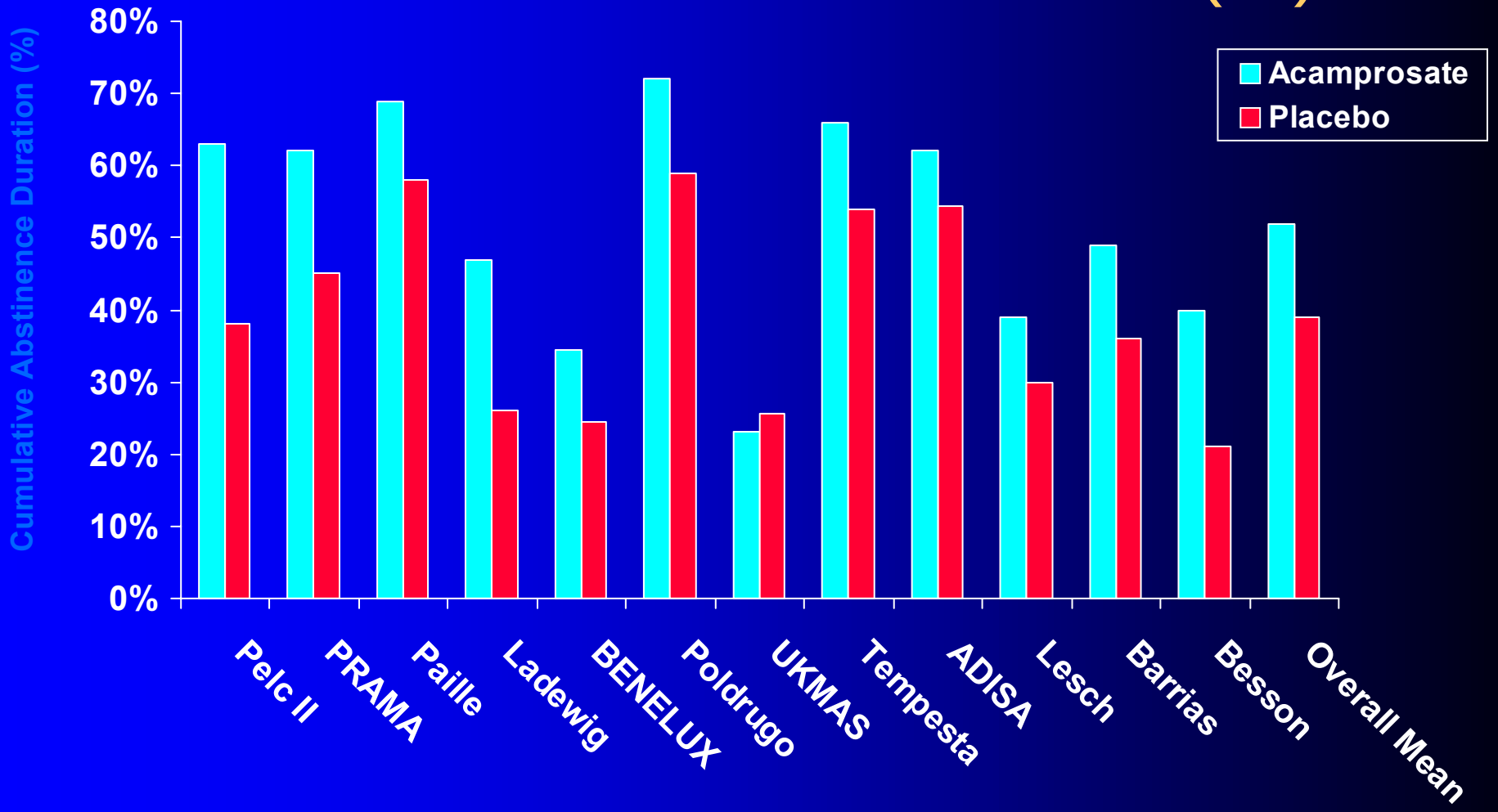
Acamprosate European Trials: Rate of Complete Abstinence (%)



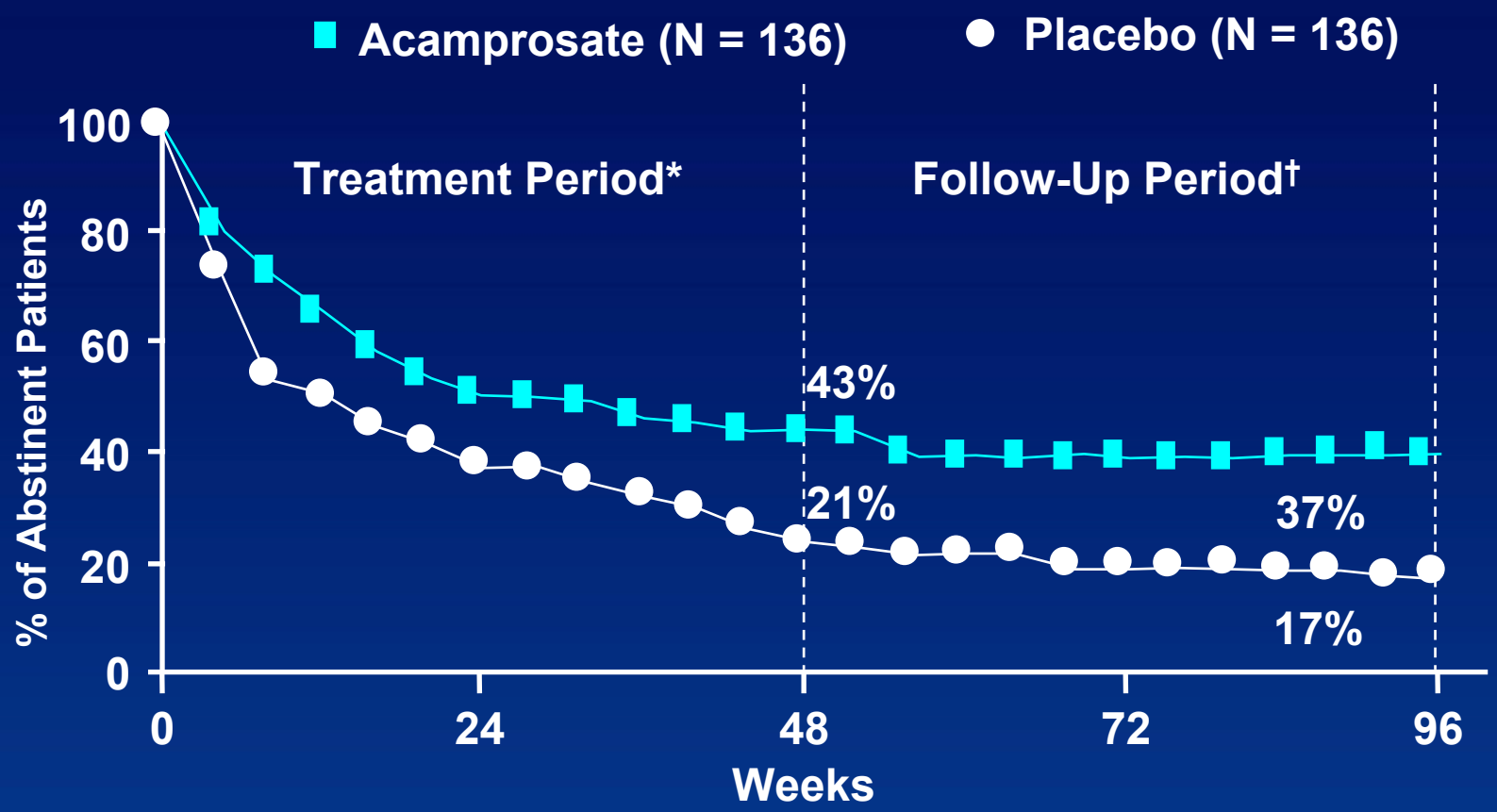
Acamprosate European Trials: Days to First Drink



Acamprosate European Trials: Cumulative Abstinence Duration (%)



Acamprosate Improves Abstinence in Alcohol Dependence



*P = 0.001; †P = 0.003; 272 patients were entered into the study over 2 years; Kaplan-Meier survival analysis (survival function estimate); abstinence for the treatment and follow-up periods.

Sass et al. *Arch Gen Psychiatry.* 1996;53:673.

Acamprosate Pharmacokinetics I

Bioavailability	**11%**
T_{max}	**3-8 hours**
C_{max}	**180 ng/mL**
C_{max} (steady state)	**350 ng/mL (5 days)**
Food Effect	**Minimal (can be taken with food)**
Plasma Protein Binding	**Negligible**
Metabolism	**None (eliminated via kidneys)**
$t_{1/2}$ (steady state)	**20-33 hours**
Volume Distribution (following IV administration)	**72-109 L (approx. 1 L/kg)**

Campral is a registered trademark of Merck Santé
Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Acamprosate Pharmacokinetics II

- No significant effects on PK parameters due to
  - gender or age
  - ethanol use or dependence
  - mild-moderate hepatic disease

- Adjustments in of renal failure:

Severity	Creatinine Clearance	Dose Adjustment
Mild	51-70	None needed
Moderate	30-50	Reduce by 50%
Severe	< 30	Contraindicated

Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Acamprosate: Drug Interactions

- **No adverse drug interactions with**
  - **Ethanol**
  - **Disulfiram**
  - **Antidepressants**
  - **Anxiolytics**
  - **Antipsychotics**
  - **Hypnotics**
  - **Opioids**

EXCEPT… (see next slide)

Mason. *J Clin Psychiatry*. 2001;62(suppl 20):42

Acamprosate-Naltrexone Interaction

- **Combining acamprosate with naltrexone increases acamprosate plasma concentration about 10%**
- **Combination may have synergistic effects on treatment efficacy**

Mason. *J Clin Psychiatry*. 2001;62(suppl 20):42; Johnson et al., 2002

Acamprosate: No cytochrome p450 effects

- **No induction of CYP1A2 or CYP 3A4 systems**
- **No inhibition of CYP1A2, 2C9, 2D6, 2E1, or 3A4**

Acamprosate not Addictive

Post-Marketing Surveillance

- **No evidence or Rx diversion, misuse, IV use, smoking, snorting of acamprosate.**
- **No self-administration by animals or human volunteers**
- **No discontinuation/withdrawal syndrome**
- **No effect on ethanol metabolism**
- **No effect on cognitive function**

Campral is a registered trademark of Merck Santé
Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Acamprosate Common Spontaneously Reported Adverse Events in Placebo-Controlled Trials*

Event	*Acamprosate (n=2019)†*	*Placebo (n=1706)*
Diarrhea	16%	10%
Asthenia	6%	5%
Nausea	4%	3%
Pruritus	4%	3%
Flatulence	3%	2%

*Incidence ≥3% in acamprosate 1998 mg/d group and greater than placebo in controlled clinical studies.
†Includes 397 patients treated with acamprosate 1332 mg/d and 1281 patients treated with acamprosate 1998 mg/d; also includes 258 patients treated with acamprosate 2000 mg/d and 83 patients treated with acamprosate 3000 mg/d, using a different dosage strength and regimen.

Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Acamprosate Safety: Lab & Vital Signs

No Clinically Relevant Differences vs Placebo in:

- **Laboratory abnormalities**
- **Electrocardiographic results**
- **Vital signs**
- **Body weight**

Acamprosate SAE's: Suicide Thought, Attempt, Death

- **RCT rates of ideas, attempts, suicides:**
  - **Study duration ≤6 months: 1.4% ACAMP vs. 0.5% PBO ($p < 0.05$)**
  - **Study duration 1 year: 2.4% ACAMP vs. 0.8% PBO ($p < 0.05$)**
- **RCT suicide rates (p = NS): 0.13% ACAMP v. 010% PBO**
- **Alcoholics have 10x elevated suicide rate**
- **Monitor for depression, suicidal ideas**

Source: Campral Prescribing Information. Forest Pharmaceuticals, Inc.

Summary of Cumulative Evidence Scores (CES)

Modality	Rank	CES	N	Mean Severity*
Brief Intervention	1	390	34	2.47
Motivational Enhancement	2	189	18	2.72
acamprosate	3	116	5	3.80
Community Reinforcement	4.5	110	7	3.43
Self-Change Manual (bibliotherapy)	4.5	110	17	2.59
naltrexone	6	100	6	3.17
Behavioral Self Control Training	7	85	31	2.91
Behavior Contracting	8	64	5	3.60
Social Skills Training	9	57	20	3.80
Behavioral Marital Therapy	10	44	9	3.44
Aversion Therapy (nausea)	11	36	6	3.83
Cognitive therapy	13	21	6	3.70
Family therapy	14.5	15	4	3.25
Client Centered Counseling	18	5	8	3.38

* 1 Risky/heavy drinker 2 Alcohol Abuse 3 Treatment seeking for alcohol problems 4 Alcohol Dependent

Miller WR, Wilbourne PL, Hettema JE. What works? A summary of Alcohol Treatment Outcome Research. In WR Miller & R Hester: Handbook of Alcoholism Treatment Approaches: Effective Alternatives, 3e (2003)

Summary of Cumulative Evidence Scores (CES) Ineffective Treatments

Modality	Rank	CES	N	Mean Severity*
Education (lectures, tapes, films)	48	- 443	39	2.44
General Alcoholism Counseling	47	- 284	28	3.22
Confrontational Counseling	45	-183	12	3.00
Relaxation Training	44	- 152	18	3.06
Anxiolytic Medication	39	- 98	15	3.40
Twelve Step Facilitation	37	- 82	6	3.67
Hypnosis	31	- 41	4	3.75
Relapse Prevention	29	- 38	22	3.23
Group Process Psychotherapy	27	- 34	3	2.67
Non-Behavioral Marital Therapy	26	- 33	8	3.63
disulfiram	22	- 6	27	3.69
Exercise	20	- 3	3	2.00

* 1 Risky/heavy drinker 2 Alcohol Abuse 3 Treatment seeking for alcohol problems 4 Alcohol Dependent

Miller WR, Wilbourne PL, Hettema JE. What works? A summary of Alcohol Treatment Outcome Research. In WR Miller & R Hester: Handbook of Alcoholism Treatment Approaches: Effective Alternatives, 3e (2003)

Practical Considerations: Acamprosate for Treating Alcoholism

- Usual dosage: two 333-mg tablets TID
- 5 d to steady-state plasma concentrations
- Use with psychosocial tx
- Abstain 4-7 days prior to starting
- Goal should be abstinence
- Duration of treatment: unknown; most recommend 90-360 d
- Contraindicated in pregnancy

Combining Naltrexone and Acamprosate in Relapse Prevention of Alcoholism

- 160 subjects randomized to placebo, placebo + naltrexone, acamprosate + placebo, naltrexone + acamprosate
- 50 mg naltrexone, 1998 mg acamprosate, placebo given for 12 weeks
- Abstinence and relapse to heavy drinking evaluated

Kiefer et al. *Arch Gen Psych.* 2003;60:92.

Dosage and Administration: Compliance Enhancement

- **Acamprosate available in blistered Dose Pak with 7 days Rx in tear off sheets & education materials, as well as usual stock bottle**
- **Blister packs known to enhance compliance in multiple dose/day Rx's**

Source: Forest Pharmaceuticals, Inc.

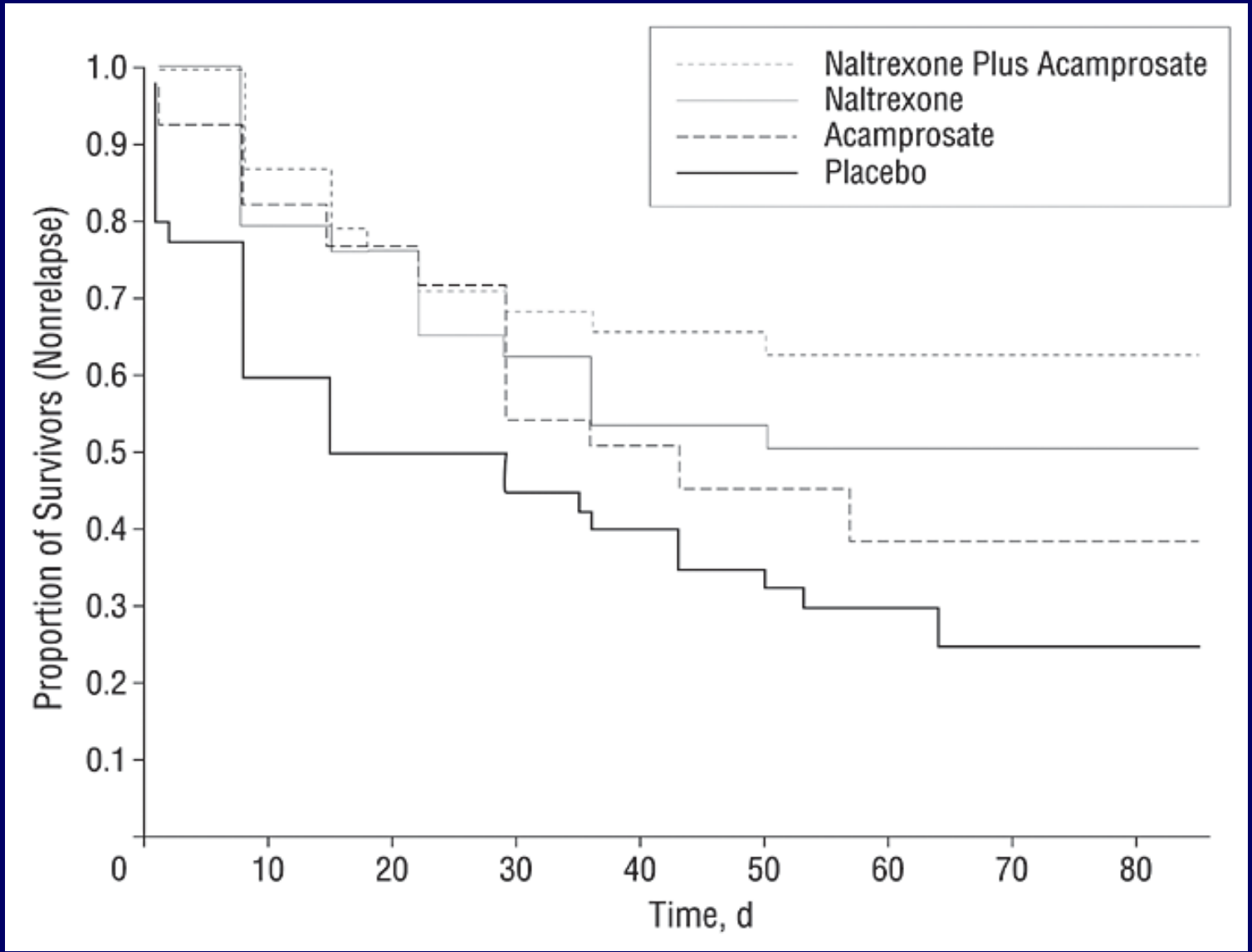
New Medication Studies I

- SSRIs
  - Two studies have shown early onset/Type B alcoholics don't benefit or drink more
- Ondansetron
  - One RCT showed decreased drinking
- Topiramate
  - One RCT showed decreased drinking
  - May be effective in early onset drinkers

New Medication Studies II

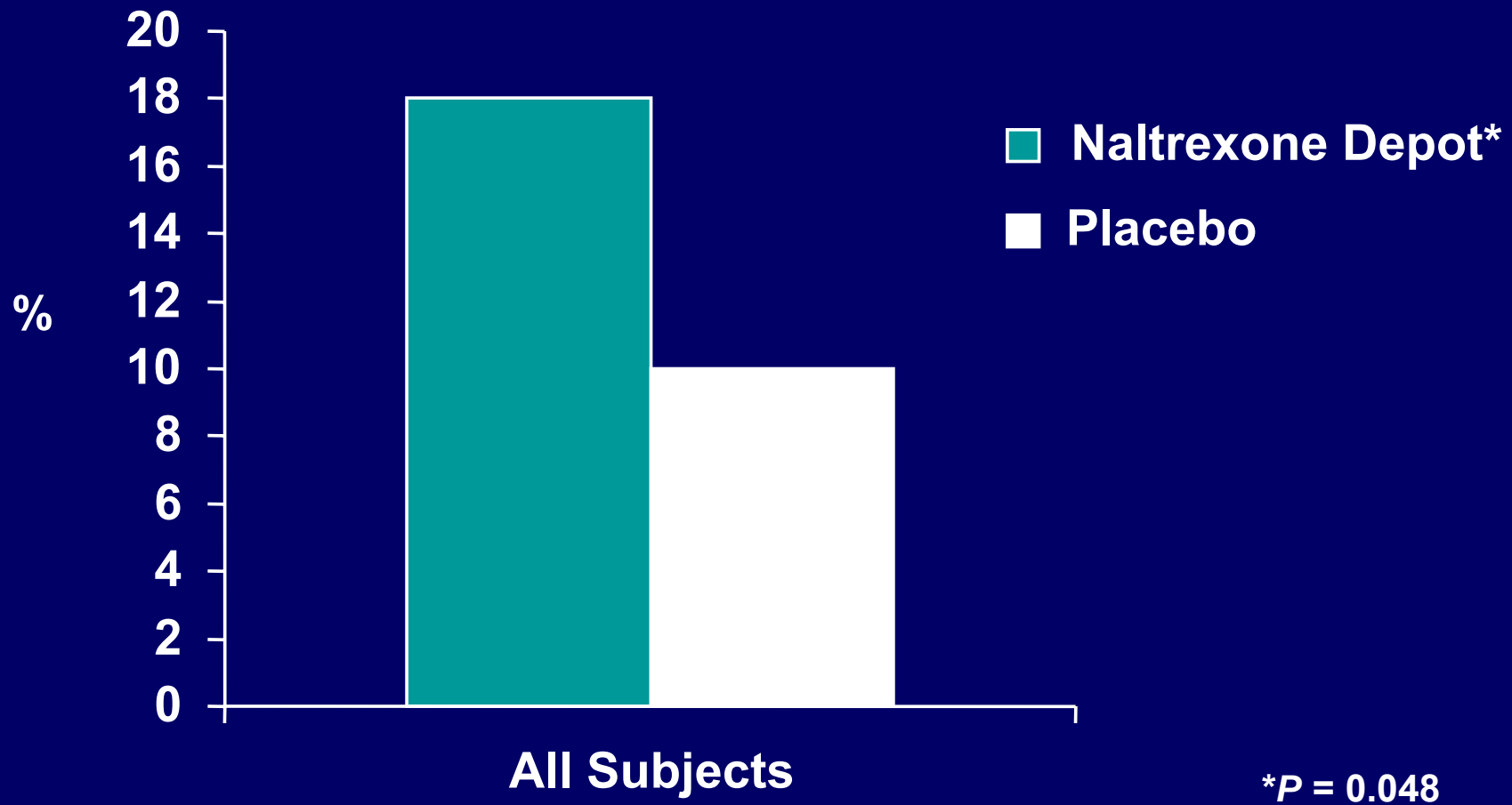
- Naltrexone depot
  - 3 published clinical trials
  - Monthly injections of PLG microspheres
  - Serum NTX concentrations more stable
  - ? If lower adverse effect rate but good compliance
  - Some injection site rxns but most mild
- Kudzu extract
  - One small clinical trial showed decreased drinking

Combination Acamprosate and Naltrexone Tx



ACER 2002

Depot Naltrexone (DAS) and Abstinence (3 Month Data)



*P = 0.048

Kranzler et al. *Alcohol Clin Exp Res.* 2004;28:1051.

Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence

A Randomized Controlled Trial

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Stephanie S. O'Malley, PhD
David R. Gastfriend, MD
Helen M. Pettinati, PhD
Bernard L. Silverman, MD
John W. Loewy, PhD
Elliot W. Ehrich, MD
for the Vivitrex Study Group

Context Alcohol dependence is a common disorder associated with significant morbidity and mortality. Naltrexone, an opioid antagonist, has been shown to be effective for treatment of alcohol dependence. However, adherence to daily oral pharmacotherapy can be problematic, and clinical acceptance and utility of oral naltrexone have been limited.

Objective To determine efficacy and tolerability of a long-acting intramuscular formulation of naltrexone for treatment of alcohol-dependent patients.

Design, Setting, and Participants A 6-month, randomized, double-blind, placebo-controlled trial conducted between February 2002 and September 2003 at 24 US public hospitals, private and Veterans Administration clinics, and tertiary care medical centers. Of the 899 individuals screened, 627 who were diagnosed as being actively drinking alcohol-dependent adults were randomized to receive treatment and 624 received at least 1 injection.

Intervention An intramuscular injection of 380 mg of long-acting naltrexone (n = 205) or 190 mg of long-acting naltrexone (n = 210) or a matching volume of placebo (n = 209) each administered monthly and combined with 12 sessions of low-intensity psychosocial intervention.

Main Outcome Measure The event rate of heavy drinking days in the intent-to-treat population.

Results Compared with placebo, 380 mg of long-acting naltrexone resulted in a 25% decrease in the event rate of heavy drinking days ($P = .03$) and 190 mg of naltrexone resulted in a 17% decrease ($P = .07$). Sex and pretreatment abstinence each showed significant interaction with the medication group on treatment outcome, with men and those with lead-in abstinence both exhibiting greater treatment effects. Discontinuation due to adverse events occurred in 14.1% in the 380-mg and 6.7% in the 190-mg group and 6.7% in the placebo group. Overall, rate and time to treatment discontinuation were similar among treatment groups.

Conclusions Long-acting naltrexone was well tolerated and resulted in reductions in heavy drinking among treatment-seeking alcohol-dependent patients during 6 months of therapy. These data indicate that long-acting naltrexone can be of benefit in the treatment of alcohol dependence.

JAMA. 2005;293:1617-1625 www.jama.com

ALCOHOL DEPENDENCE IS A MAJOR public health problem, which worldwide is the fourth leading cause of disability.[1] Alcohol dependence is present in approximately 4% of the US adult population,[2] is common among primary care patients,[3,4] and may contribute to more than 100 000 preventable deaths per year.[5] Addiction counseling, behavioral treatments, and self-help groups (eg, Alcoholics Anonymous) are the primary interventions used to treat alcohol dependence in the United States. Although these treatments are often effective, a substantial number of patients fail to complete them or relapse.[6]

Similar to diabetes, hypertension, and asthma, alcohol dependence is increasingly recognized as a chronic disease in which genetic vulnerability and social and environmental factors are involved in the etiology and course of the disease.[7] As with other chronic diseases, long-term comprehensive man-

See also Patient Page.

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The Vivitrex Study Group members participating in this trial are listed at the end of the article.
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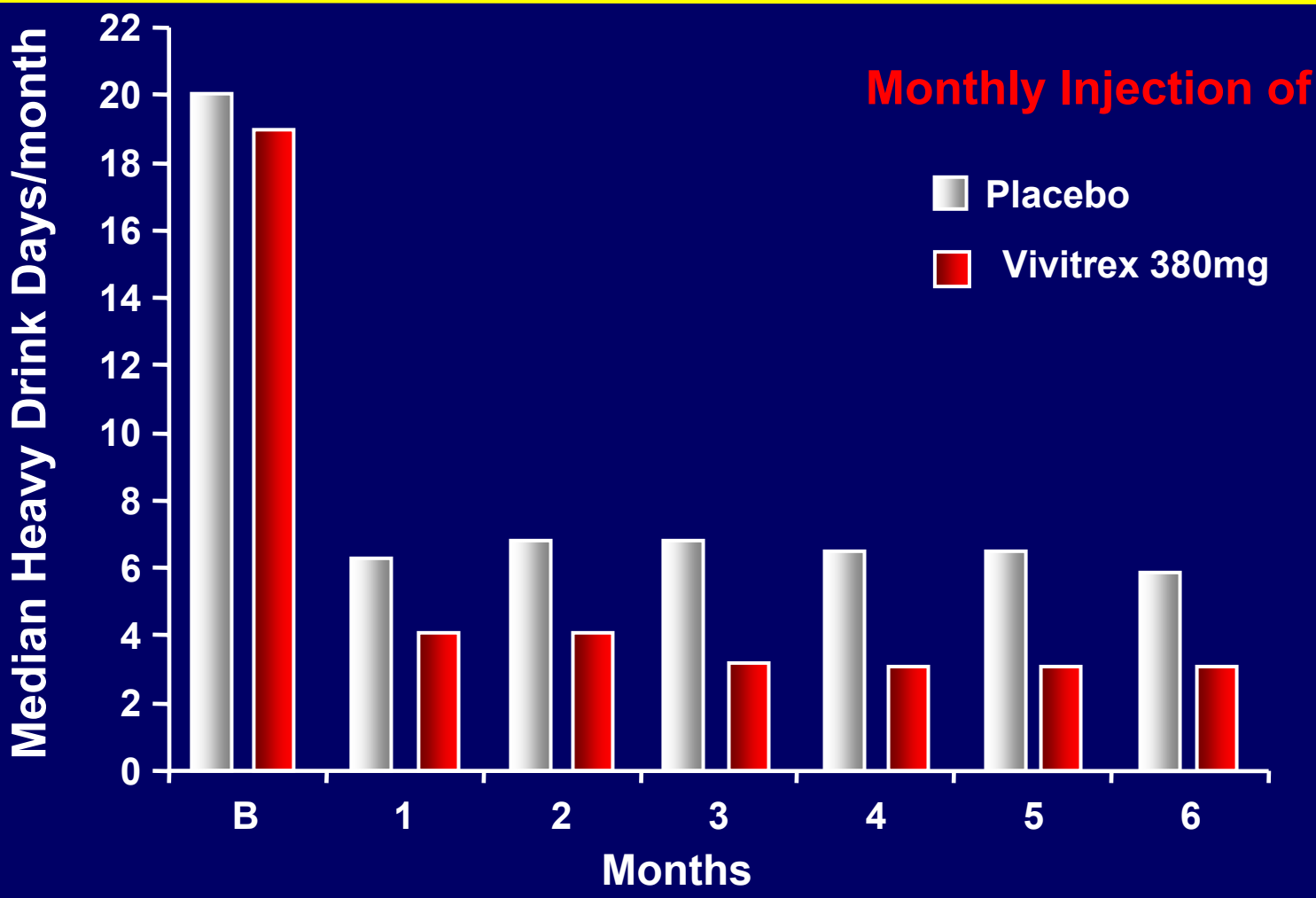
Depot Naltrexone (Alkermes):
Reduction in Heavy Drinking Days/ Month



Garbutt et al. JAMA. 2005;293:1617-1625.

SUMMARY

- Strong biological basis for alcohol use
- Disulfiram ok, compliance poor
- Naltrexone effective, response ? genetic
- Acamprosate effective
- Other Rx intriguing: topiramate, ondansetron, depot naltrexone, etc.